Tissue Mechanics Orchestrate Wnt-Dependent Human Embryonic Stem Cell Differentiation.

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Authors: Laralynne Przybyla, Johnathon N Lakins, Valerie M Weaver

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Public Summary:
Embryonic stem cells have the potential to become any cell type in the adult organism, but coaxing them to a specific fate continues to be a challenge for researchers. While many of the soluble signals involved in patterning the early embryo are well-established, only recently have tools been available to study how biophysical cues synchronize with other signals in the microenvironment to specify cell fate during development. Mechanical signals have been implicated in controlling stem cell fate in a number of contexts, but the molecular mechanisms involved are often not well-defined. By taking cues from embryonic development, we have identified a key role for mechanical signals in driving differentiation of human embryonic stem cells (hESCs) toward mesoderm. This manuscript describes our experiments that utilize genetic and pharmacologic manipulation to identify molecular mechanisms whereby tissue tension directs stem cell fate and demonstrated how hESC differentiation protocols can be optimized to direct early progenitor specification.

Scientific Abstract:
Regenerative medicine is predicated on understanding the mechanisms regulating development and applying these conditions to direct stem cell fate. Embryogenesis is guided by cell-cell and cell-matrix interactions, but it is unclear how these physical cues influence stem cells in culture. We used human embryonic stem cells (hESCs) to examine whether mechanical features of the extracellular microenvironment could differentially modulate mesoderm specification. We found that, on a hydrogel-based compliant matrix, hESCs accumulate beta-catenin at cell-cell adhesions and show enhanced Wnt-dependent mesoderm differentiation. Mechanistically, Src-driven ubiquitination of E-cadherin by Cbl-like ubiquitin ligase releases P120-catenin to facilitate transcriptional activity of beta-catenin, which initiates and reinforces mesoderm differentiation. By contrast, on a stiff hydrogel matrix, hESCs show elevated integrin-dependent GSK3 and Src activity that promotes beta-catenin degradation and inhibits differentiation. Thus, we found that mechanical features of the microenvironmental matrix influence tissue-specific differentiation of hESCs by altering the cellular response to morphogens.